Int Health 2017; **9**: 148–155
doi:10.1093/inthealth/ihx011

COMMENTARY

Serious bacterial infections in neonates: improving reporting and case definitions

Stefania Vergnano[a,1,*], Anna C. Seale[b,c], Elizabeth J.A. Fitchett[b], Mike Sharland[a] and Paul T. Heath[a]

[a]*Paediatric Infectious Disease Research Group, Department of Infection and Immunity, St George's University of London, Jenner wing, London, UK;* [b]*MARCH Centre, London School of Hygiene & Tropical Medicine, London, UK;* [c]*The Farr Institute of Health Informatics Research, University College London, London, UK*

[1]Present Address: Bristol Royal Hospital For Children, Department of Paediatric Infectious Diseases, Bristol, UK
*Corresponding author: Tel: +44 (0) 77 7078 8880; E-mail: stev@doctors.org.uk

Received 11 November 2016; revised 29 March 2017; editorial decision 30 March 2017; accepted 21 April 2017

Neonatal infections affect about 7 million neonates causing over 600 000 deaths every year. Estimating the burden is challenging as there are multiple reporting criteria and definitions for serious bacterial infections in neonates. Essential criteria for reporting serious neonatal bacterial infections have recently been published as the STROBE-NI checklist and, in the context of maternal vaccination, definitions have been published by the Brighton Collaboration Global Alignment of Immunization safety Assessment in pregnancy (GAIA) project. Standardisation of reporting criteria is essential to allow data comparability. This an important step in providing a clearer picture of the burden of serious bacterial infections in neonates and a welcome progress for guiding new investments in interventions.

Keywords: Bacteremia, Bacterial infection, Infant, Neonatal infections, Newborn, Septicemia

In the neonatal period over 600 000 deaths every year are directly due to infections, with the highest burden in low and middle income countries (LMICs).[1] The burden of clinically defined possible serious bacterial infections in neonates is high. Meta-analyses of studies from sub Saharan Africa, South Asia and Latin America estimate that 6.9 million neonates need treatment for possible serious bacterial infections each year:[2] this is over 3 times the yearly burden of new HIV infections in children under 15 years of age.[3] Neonatal infections and mortality are highest in the first 24 hours after birth and are disproportionally more common in low income countries, where most births occur at home. In these settings capturing the burden of early infections and deaths is logistically challenging, even as part of research studies, because births and deaths are regularly not reported.

Global estimates that specifically reflect aetiology, antimicrobial resistance patterns and outcome have never been possible due limited access to diagnosis and treatment in the highest burden settings, as well as inconsistency of clinical diagnosis. Few countries have adequate surveillance systems for neonatal infection and the burden of impairment after neonatal infection is also not well established.[4]

Definitions of serious bacterial infection in neonates vary and there are no universally accepted standards. Underlying this are the challenges of diagnosing serious bacterial infection, which is usually based on simple clinical algorithms due to limited laboratory facilities in LMICs. Even where available, blood cultures are often negative due to small volume samples and frequent contamination. Molecular methods using nucleic-acid extraction are highly sensitive, but bring their own challenges of interpretation and are mostly limited to research settings.

Tables 1, 2 and 3 illustrate the plethora of definitions and reporting criteria used by current neonatal networks and epidemiological units, mostly based in high income countries. Substantial differences in definitions of serious bacterial infections make comparisons between studies difficult, even when raw data are compared, because different indicators are collected. Some definitions and criteria are widely used to inform research studies, but are often adapted to local circumstances rendering the resulting data incomparable.

The variation in clinical definitions and research reporting criteria for neonatal infections is partly due to the existence of a number of types of surveillance networks, which have been designed for different purposes. These include clinical networks monitoring all aspects of neonatal care (e.g. International Neonatal Network, iNEO), networks which focus on infections in (mostly adult) intensive care settings and epidemiological networks such as those coordinated by the US Centers for Disease Control (CDC) and the European Medicine Agency (EMA), which supervises the development and evaluation of new and existing drugs. There are also a limited number of surveillance groups focusing specifically on

Table 1. Comparison of definitions for culture proven blood stream infections

Current network definitions	NEOKISS; European Centre for Disease Control (ECDC)	European Medicine Agency (EMA)	Centers for Disease Control and Prevention/National healthcare safety network (CDC-NHSN); Canadian Neonatal Network (CNN); International Nosocomial Infection Control Consortium (INICC)	Egyptian Neonatal Network (EGNN)	Australian and New Zealand Neonatal Network (ANZNN)	Neonatal Data Analysis Unit (NDAU)	Global Alignment of Immunization safety Assessment in pregnancy (GAIA) - Level 1 definition; European Neonatal Network (ENN); Oxford Vermont Neonatal Network (OVN); Neonatal Infection Surveillance Network (NEONIN)
Microbiological criteria:[a]				3 of the following:			
Pathogen isolated from blood culture or CSF AND Pathogen not related to infection in other site	✓	✓	✓	✓ OR Positive CRP or abnormal haemogram	✓	✓	✓ Recognized pathogen identified using a validated method and from a normally sterile site
Number of additional criteria:	AND at least two of:	AND at least two of:	At least one of:	AND two or more clinical signs of sepsis (not specified)	AND	AND at least three of:	
Patients receiving antibiotics for at least 5 days (or <5 days if transferred or died before completion of these 5 days)				✓	✓		
Clinical signs:				Clinical picture consistent with neonatal infection			
Temperature instability	✓ Fever or hypothermia or temperature instability.	✓	✓			✓	
Cardiovascular signs	✓ Tachycardia or new or more frequent bradycardia.	✓	✓ Bradycardia			✓ Hypotension ✓ Fall in urine output	

Continued

Table 1. *Continued*

Current network definitions	NEOKISS; European Centre for Disease Control (ECDC)	European Medicine Agency (EMA)	Centers for Disease Control and Prevention/National healthcare safety network (CDC-NHSN); Canadian Neonatal Network (CNN); International Nosocomial Infection Control Consortium (INICC)	Egyptian Neonatal Network (EGNN)	Australian and New Zealand Neonatal Network (ANZNN)	Neonatal Data Analysis Unit (NDAU)	Global Alignment of Immunization safety Assessment in pregnancy (GAIA) - Level 1 definition; European Neonatal Network (ENN); Oxford Vermont Neonatal Network (OVN); Neonatal Infection Surveillance Network (NEONIN)
Respiratory distress	✓ Increased oxygen requirement (intubation)	✓ Tachypnoea				✓ Increased oxygen requirement or respiratory support	
Apnoea	✓ New or more frequent apneas.	✓	✓			✓ New or more frequent apnoeas or bradycardias	
Signs of poor perfusion	✓ CRT>2 s ✓ Skin color (only when recapillarization time is not used)	✓ Sclerema ✓ Mottled skin				✓ CRT>2 s or impaired peripheral perfusion	
Feeding intolerance		✓				✓ Ileus	
Central nervous system signs	✓ Unstable condition, apathy	✓ Lethargy, irritability and hypotonia				✓ Lethargy	
Glucose intolerance	✓ New hyperglycema.	✓				✓ Glucose intolerance	
Metabolic acidosis (BE ≤10 mEq/L)	✓ Unexplained metabolic acidosis	✓ or lactate>2 mMol/L				✓ Unexplained metabolic acidosis	
Laboratory criteria:		AND two of:					
Abnormal platelet count.		Plt<1×10^{14}					
Abnormal WCC		I/T>0.2					
Abnormal CRP or interleukin	✓ Increased CRP, interleukin (not included in ECDC definition)	✓ CRP>15 mg/L or procalcitonin ≥2 ng/ml					

BE: base excess; CRP: C reactive protein; CRT: capillary refill time; CSF: cerebrospinal fluid; I/T: immature to total neutrophil ratio; mEq/L: milliequivalents per litre; Plt: platelet; WCC: white cell count.
Infection networks: INICC: international nosocomial infection control consortium (international healthcare associated infection database and infection control packages): NEOKISS: German neonatal infections network including only very low birth weight babies (birth weight<1500g) – developed from adult and paedaitric intensive care and focusing on health care associated infections; NEONIN; neonatal infection surveillance network (UK, Australia, Greece and Estonia - neonatal infection database collecting data on all neonatal infections in all infants admitted to neonatal units).
Neonatal networks (including neonatal infection definitions): ANZNN: Australian and New Zealand neonatal network; CNN: Canadian neonatal network (national neonatal network); EGNN: Egyptian neonatal network; ENN: European neonatal network (neonatal network); NDAU: neonatal data analysis unit (UK based national database); OVN: Oxford Vermont neonatal network.
Primarily epidemiological and trial units: (E)CDC: (European) centre for disease control (epidemiological purposes); EMA: European Medicine Agency; GAIA: global alignment of immunization safety assessment in pregnancy; NHSN: national healthcare safety network (part of CDC tracking health care associated infections).
[a] EMA and ANZNN also include positive PCR/antigen testing.

Table 2. Comparison of definitions for blood stream infections when common commensals are isolated

Bloodstream infection definition criteria	NEOKISS; European Medicine Agency (EMA); European Centre for Disease Control (ECDC)	Centers for Disease Control and Prevention/National healthcare safety network (CDC-NHSN); Canadian Neonatal Network (CNN)[a]	International Nosocomial Infection Control Consortium (INICC)	European neonatal network (ENN); Oxford Vermont neonatal network (OVN)	Neonatal Data Analysis Unit (NDAU)	Australian and New Zealand Neonatal Network (ANZNN)	Global Alignment of Immunization safety Assessment in pregnancy (GAIA) – Level 1 definition
Microbiological criteria:							
At least 2 or more positive BC with the same organism drawn on separate occasions (within 2 days of each other)	CoNS isolated in blood culture as sole pathogen	✓	✓	CoNS recovered from a blood culture obtained from either a central line or peripheral blood sample, and/or is recovered from CSF obtained by lumbar puncture, ventricular tap or ventricular drain	Mixed growth or skin commensal	✓	✓
Number of additional criteria:	AND at least two of:	AND at least one of:	AND at least three of:	AND			
Patient receiving antibiotics for at least 5 days (or <5 days if transferred or died before completion of these 5 days)				✓		✓	
Clinical signs:				AND at least 1 of:		AND clinically septic	AND at least 1 of:
Temperature instability	✓ Fever or hypothermia or temperature instability	✓ Fever, hypothermia	✓ Fever	✓ Temperature instability	✓ Temperature instability		✓ Temperature ≥37.5°C or <35.5°C
Cardiovascular signs	✓ Tachycardia or new or more frequent bradycardia	✓ Bradycardia	✓ Hypotension	✓ Hemodynamic instability	✓ Hypotension		✓ Tachycardia or new or more frequent episodes of bradycardia
Signs of poor perfusion	✓ CRT>2 s or skin color (only when recapillarization time is not used)		✓ Chills		✓ Impaired peripheral perfusion (CRT>3 s, pallor/mottling/ core peripheral temperature gap >2°C. Fall in urine output		✓ Pallor or poor perfusion or hypotension
Apnoeas	✓ New or more frequent	✓		✓ OR worsening respiratory distress	✓ Clinically relevant OR bradycardia episodes		✓ Increased oxygen requirement or increased requirement for ventilatory support

Continued

Table 2. *Continued*

Bloodstream infection definition criteria	NEOKISS; European Medicine Agency (EMA); European Centre for Disease Control (ECDC)	Centers for Disease Control and Prevention/National healthcare safety network (CDC-NHSN); Canadian Neonatal Network (CNN)[a]	International Nosocomial Infection Control Consortium (INICC)	European neonatal network (ENN); Oxford Vermont neonatal network (OVN)	Neonatal Data Analysis Unit (NDAU)	Australian and New Zealand Neonatal Network (ANZNN)	Global Alignment of Immunization safety Assessment in pregnancy (GAIA) – Level 1 definition
Feeding intolerance				✓	✓ OR Ileus		✓ Difficulty in feeding or abdominal distention.
Metabolic acidosis (BE ≤10 mEq/L)	✓				✓		✓
Glucose intolerance	✓ Hyperglycaemia	AND			✓		
Other signs of bloodstream infection	✓ Increased oxygen, requirement (intubation)	Clinical signs and laboratory results are not related to an infection in another site			Tachypnea or clinically relevant increase in oxygen requirement or ventilator support		
Central nervous system signs	✓ Unstable condition, apathy				Lethargy, irritability or poor handling		✓ Lethargy or moving only when stimulated or hypotonia or irritability
Laboratory criteria:	AND at least one of:						
Abnormal CRP	CRP>2.0 mg/dl other interleukin						✓ Increased number of inflammatory markers (CRP, procalcitonin)
Abnormal WCC	I/T ratio>0.2 (immature granulocytes/total granulocytes) OR leukocytopaenia (without erythroblasts)					✓	✓ OR I/T ratio > 0.2.
Abnormal platelet count	Thromocytopaenia					✓ Thromocytopaenia	✓

BC: blood cultures; BE: base excess; CoNS: coagulase negative Staphylococci; CSF: cerebrospinal fluid; CRP: C reactive protein; CRT: capillary refill time; I/T: immature to total neutrophil ratio; mEq/L: milliequivalents per litre; WCC: white cell count.
Infection networks: INICC: international nosocomial infection control consortium (international healthcare associated infection database and infection control packages); NEOKISS: German neonatal infections network including only very low birth weight babies (birth weight<1500g) – developed from adult and paedaitric intensive care and focusing on health care associated infections.
Neonatal networks (including neonatal infection definitions): ANZNN: Australian and New Zealand neonatal network; CNN: Canadian neonatal network (national neonatal network); ENN: European neonatal network; NDAU: neonatal data analysis unit (UK based national database); OVN: Oxford Vermont neonatal network.
Primarily epidemiological and trial units: (E)CDC: (European) centre for disease control (epidemiological purposes); EMA: European medicine agency (providing definitions used in clinical trials); GAIA: global alignment of immunization safety assessment in pregnancy; NHSN: national healthcare safety network (part of CDC tracking health care associated infections).
[a] CNN has several definition criteria, one is listed in the table, the others are as follows: 1. Fever, chills or hypotension (or fever, hypothermia, apnoea or bradycardia) and common skin contaminant isolated from a blood culture in a patient with intravascular access device AND the physician institutes appropriate antimicrobial therapy for at least 5 days; 2. The three clinical signs above and common skin contaminant isolated from patient's blood culture and physician institutes appropriate antimicrobial therapy for at least 5 days; 3. One of the three clinical signs above and positive antigen test on blood and organism is not related to infection in another site.

Table 3. Comparison of definitions for culture negative blood stream infections (possible serious bacterial infection)

Definition for culture negative blood stream infection	NEOKISS; European Centre for Disease Control (ECDC)	European Medicine Agency (EMA)	Centers for Disease Control and Prevention/ National Healthcare Safety Network (CDC-NHSN); Canadian Neonatal Network (CNN)	International Nosocomial Infection Control Consortium (INICC)	Egyptian Neonatal Network (EGNN)	Young Infant Clinical Study Group – WHO (YICSG-WHO); Global Alignment of Immunization safety Assessment in pregnancy (GAIA)[a] Level 3 definition	Global Alignment of Immunization safety Assessment in pregnancy (GAIA) Level 2 definition
	All of the following:		All of the following:	In presence of a central line:	Three of the following:	GAIA any two of the following; YICSG-WHO at least one of the following:	
Antimicrobial therapy for bloodstream infection for at least 5 days	✓		✓	✓	✓		
Lack of positive microbiology data or no organism detected	✓	✓	✓	✓	✓ Positive CRP or abnormal haemogram		✓
No apparent infection at another site	✓	✓	✓	✓	✓ Risk factors for sepsis (chorioamnionitis, prematurity)		
Number of necessary criteria	AND at least two of:	At least two clinical + two laboratory signs:	AND at least one of:	AND at least one of:	Two clinical signs of sepsis (not specified):		Three or more of:
Clinical signs:							
Temperature instability (fever or hypothermia)	✓	✓	✓	✓		✓ Temperature ≥37.5°C or <35.5°C	✓ Temperature ≥37.5°C or <35.5°C
Signs of poor perfusion	✓ CRT time>2s OR skin color (only when CRT is not used)			✓ Hypotension oliguria			✓ Pallor or poor perfusion or hypotension
Apnoea	✓ New or more frequent	✓	✓				✓
Signs of respiratory distress	✓ Increased O_2 requirement (intubation)	✓ Tachypnoea (mean respiratory rate (RR)>2 SD above normal for age) or increased oxygen requirements or requirement for ventilation support				✓ RR≥60. Severe chest indrawing. Cyanosis (GAIA only)	✓ Increased oxygen requirement or increased requirement for ventilatory support
Poor feeding		✓ Feeding intolerance, poor sucking abdominal distention				✓ History of difficulty feeding	✓ Difficulty in feeding or abdominal distention

Continued

Table 3. *Continued*

Definition for culture negative blood stream infection	NEOKISS; European Centre for Disease Control (ECDC)		European Medicine Agency (EMA)		Centers for Disease Control and Prevention/ National Healthcare Safety Network (CDC-NHSN); Canadian Neonatal Network (CNN)		International Nosocomial Infection Control Consortium (INICC)	Egyptian Neonatal Network (EGNN)	Young Infant Clinical Study Group – WHO (YICSG-WHO); Global Alignment of Immunization safety Assessment in pregnancy (GAIA)[a] Level 3 definition		Global Alignment of Immunization safety Assessment in pregnancy (GAIA) Level 2 definition	
Central nervous system signs	✓	Unstable condition, apathy	✓	Irritability, lethargy and hypotonia					✓	Movement only when stimulated. History of convulsions	✓	Lethargy or moving only when stimulated or hypotonia or irritability
Cardiovascular instability	✓	Tachycardia (>200/min) or new/more frequent bradycardia (<80/min)	✓	Bradycardia or tachycardia and/or unexplained persistent depression over a 0.5 h time period) or rhythm instability	✓	Bradycardia					✓	Tachycardia or new or more frequent episodes of bradycardia
Other signs of infections			Petechial rash, sclerema									
Glucose intolerance	✓	Hyperglycaemia	✓	Hyperglycaemia detected at least 2 times or hypoglycaemia								
Unexplained metabolic acidosis (BE≤10 mEq/l)		✓	✓	OR increased serum lactate								✓
Laboratory parameters:												
Abnormal CRP	✓	Laboratory evidence (CRP, interleukin)	✓	Increased CRP or procalcitonin							✓	Increased number of inflammatory markers (CRP, procalcitonin)
Abnormal WCC			✓	Leucopoenia or leukocytosis or $>2\times10^{13}$ cells/l Immature to total neutrophil ratio (I/T)>0.2							✓	OR I/T ratio>0.2
Abnormal platelet count			✓	Thrombocytopoenia								✓

BE: base excess; CRP: C reactive protein; CRT: capillary refill time; I/T: immature to total neutrophil ratio; mEq/L: milliequivalents per litre; RR: respiratory rate; WCC: white cell count.
Infection networks: INICC: international nosocomial infection control consortium (international healthcare associated infection database and infection control packages); NEOKISS: German neonatal infections network including only very low birth weight babies (birth weight<1500g) – developed from adult and paedaitric intensive care and focusing on health care associated infections.
Neonatal networks (including neonatal infection definitions): CNN: Canadian neonatal network (national neonatal network); EGNN: Egyptian neonatal network; YICSG-WHO: young infant clinical study group – WHO.
Primarily epidemiological and trial units: (E)CDC: (European) centre for disease control (epidemiological purposes); EMA: European medicine agency (providing definitions used in clinical trials); GAIA: global alignment of immunization safety assessment in pregnancy; NHSN: national healthcare safety network (part of CDC tracking health care associated infections).
[a] GAIA: global alignment of immunization safety assessment in pregnancy – 3 different levels of definitions are provided depending on the data available. Level 3 definition (not meeting level 1 or 2 definition of evidence AND two or more of the following criteria): Temperature ≥37.5°C or <35.5°C; tachypnea or severe chest indrawing or grunting or cyanosis; change in level of activity; history of feeding difficulty; history of convulsions.

neonatal infection (e.g. neonIN – the UK neonatal infection surveillance network).[5] Such networks play a particularly important role in monitoring healthcare associated infections and are not necessarily restricted to high income countries. For example, the International Nosocomial Network Infection Control (INNIC) database is a global initiative that aims to monitor and reduce the rate of healthcare associated infections, particularly in LMICs, and includes neonates.[6]

Definitions used for hospitalized neonates, especially in high income countries, have limited value for early onset infection in the community or in lower level health care settings with the highest burden of disease. Simpler clinical definitions of serious bacterial infections such as the WHO young infant definition, are available and are essential for clinical decision making in low-resource settings. These have been used in some of the few available population-based studies. However, with wide variations in reporting between studies and different adaptations of the original definitions, it remains extremely challenging to reconcile differences in data for large-scale analysis of burden, aetiology and outcomes after interventions.

Addressing these issues, two recent collaborative projects have made important steps towards improved reporting of neonatal infection data. The Strengthening Publications Reporting Infections in Newborns Globally (SPRING) group was formed in 2015 with the intention of reducing some of the heterogeneity by reaching a consensus on essential reporting criteria for neonatal infection data. The group is an expert panel of clinicians, academics, researchers, epidemiologists, funders and statisticians. Following a systematic literature review, they prepared and disseminated a survey of possible reporting criteria to a large group of experts from 37 countries representing all 5 continents. The reporting criteria were then discussed in a consensus meeting and 28 final items were included in the STROBE-NI (Strengthening the Reporting of Observational Studies in Epidemiology for Neonatal Infection) checklist, published in September 2016.[7] It is hoped that the STROBE-NI criteria will not only improve reporting, but also indirectly shape research and study design. Definitions for neonatal bloodstream infections, meningitis and respiratory infections have been produced by the Brighton Collaboration Global Alignment of Immunization safety Assessment in pregnancy (GAIA) project, aiming to define neonatal infection in the context of maternal vaccine studies.[8]

As improving newborn survival gains recognition as a key global health priority, these new international guidelines will be essential in supporting quality research in serious bacterial infections and possible serious bacterial infections, estimates of the burden of disease and for the evaluation of interventions aimed at pregnant women, neonates and infants.

Authors' contributions: SV drafted the manuscript, ACS, EJAF, MS and PTH edited and contributed to successive versions of the manuscript. SV, ACS, EJAF and PTH were involved in the SPRING group and the development of the STROBE-NI guidelines. SV and PTH coordinated the GAIA working group for the definitions of neonatal infections. SV is guarantor of the paper.

Acknowledgements: The authors thank Professor Joy Lawn for the inspiration, encouragement and support for this work.

Funding: None.

Competing interests: None declared.

Ethical approval: Not required.

References

1 Liu L, Oza S, Hogan D et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet 2015;385; 430–40.

2 Seale AC, Blencowe H, Manu AA et al. Estimates of possible severe bacterial infection in neonates in sub-Saharan Africa, south Asia, and Latin America for 2012: a systematic review and meta-analysis. Lancet Infect Dis 2014:14:731–41.

3 UNAIDS. AIDS by the Numbers. Geneva, Switzerland; UNAIDS; 2016. http://www.unaids.org/sites/default/files/media_asset/AIDS-by-the-numbers-2016_en.pdf [Accessed 14 October 2016].

4 Seale AC, Blencowe H, Zaidi A et al. Neonatal severe bacterial infection impairment estimates in South Asia, sub-Saharan Africa, and Latin America for 2010. Pediatr Res 2013;74:73–85.

5 neonIN. Neonatal Infection Surveillance Network. https://www.neonin.org.uk [accessed 29 March 2017].

6 Dursun O, Ramachandran B, Villamil-Gómez W et al. Impact of a multidimensional infection control strategy on central line-associated bloodstream infection rates in pediatric intensive care units of five developing countries: findings of the International Nosocomial Infection Control Consortium (INICC). Infection 2012; 40:415–23.

7 Fitchett EJS, Seale AC, Vergnano S et al. Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection (STROBE-NI): an extension of the STROBE statement for neonatal infection research. Lancet Infect Dis 2016;16: e202–13.

8 Vergnano S, Buttery J, Cailes B et al. Neonatal infections: Case definition and guidelines for data collection, analysis, and presentation of immunisation safety data. Vaccine 2016; 34:6038–46.